# Protocol Tg 511-13-01
# NIH OBA Protocol # 1304-1230

Presentation to the Recombinant DNA Advisory Committee

June 11, 2013



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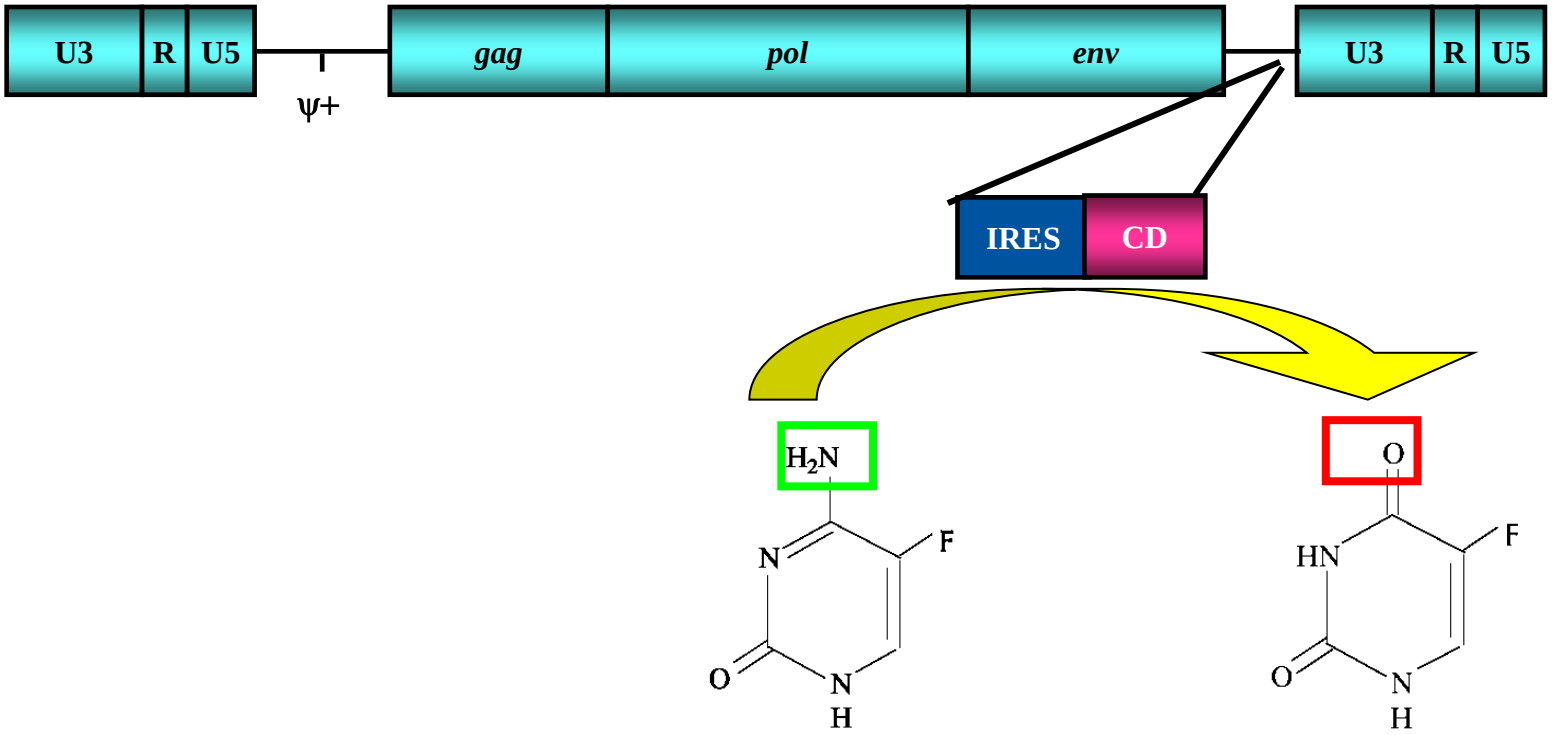
# Topics

- Toca 511 & 5-FC refresher
- Update ongoing studies Tg 511-08-01 & 11-01
- Rationale for intravenous dosing protocol
- Design of intravenous protocol
- Summary

# Toca 511

- Toca 511 is a Retroviral Replicating Vector (RRV)
- Based on Murine Leukemia Virus (MoMLV)
  - Ecotropic env changed to amphotropic env
  - Optimized cytosine deaminase (CD) gene inserted between env and 3’ LTR
    - CD catalyzes conversion of antifungal drug 5-FC to anti-neoplastic drug 5-FU
- Internal Ribosome Entry Sequence facilitates CD expression

# Schematic of Toca 511




5-FC

5-FU





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# Common Themes of all Toca 511 Studies

- Deliver vector
- Allow time for vector to integrate & spread in tumor
- Administer cycles of 5-FC orally

# Intratumoral & Surgical Resection Studies

| | Tg 511-08-01 (Intratumoral) | Tg 511-11-01 (Surgical Resection) |
|---|---|---|
| Indication | rHGG | rHGG |
| Vector | Toca 511 | Toca 511 |
| Administration | Intratumoral | Resection bed |
| Doses (TU/g) | $2.6x10^3$, $9.5x10^3$, $2.5x10^4$, $10^5$, $3.2x10^5$, $10^6$ | $9.5x10^3$, $2.5x10^4$ $10^5$, $3.2x10^5$, $10^6$ |
| Escalation | ½ log | ½ log |
| Design | 3+3 | 3+3 |
| Prodrug | 5-FC | 5-FC |
| Objectives | Safety, tolerability, MTD | Safety, tolerability, MTD |

# Tg 511 Dosing Summary

| Dose (TU/g) | Tg 511-08-01 (Intratumoral) | Tg 511-11-01 (Surgical Resection) |
|---|---|---|
| 2.6 x 10^3 | 3 | - |
| 9.5 x 10^3 | 3 | 3 |
| 2.5 x 10^4 | 9 | 4 |
| 1 x 10^5 | 5 | 6 |
| 3.2 x 10^5 | 3 | 6 |
| 1 x 10^6 | 2 | 3 |
| **Total** | **25** | **22** |

# DLTs by Dosing Cohort

| Dose (TU/g) | Tg 511-08-01 N=25 | Tg 511-11-01 N=22 |
|---|---|---|
| 2.6 x 10^3 | 0 | N/A |
| 9.5 x 10^3 | 0 | 0 |
| 2.5 x 10^4 | 0 | 0 |
| 1 x 10^5 | 0 | 1 |
| 3.2 x 10^5 | 0 | 0 |
| 1 x 10^6 | enrolling | enrolling |

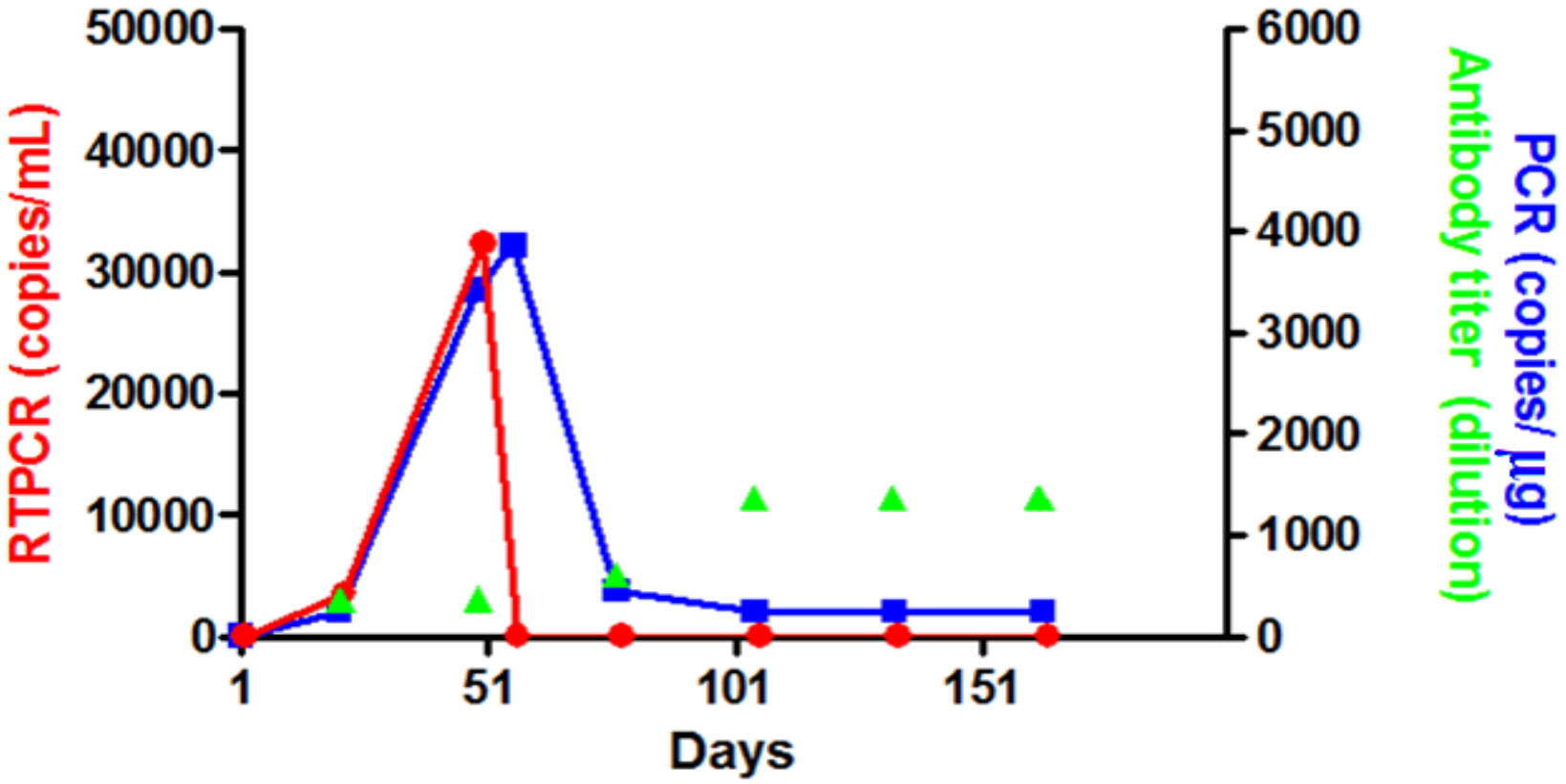
# DLT reviewed with RAC March 2013

- 70 yo male with rGBM (10^5 TU/g)
- DLT = Gr 3 weakness (Asthenia) ≈ 4 weeks after surgery
- RTPCR (plasma) → 193,000 copies/mL virus
- Intercurrent medical conditions: URI, PE
- Discharged on hospital day 4
- Repeat RTPCR 10 days after first → BLOQ virus (no specific treatment)
- RTPCR remains negative > 9 months

# Toca 511 Biodistribution

- 6/47 subjects have had quantifiable viremia (+RTPCR)
  - Not dose dependent
- All controlled viremia w/o need for antiretroviral Rx
- Viremia usually asymptomatic
- Only 2 subjects have shed vector
  - Both in saliva
  - Both low titer (BLOQ) and transient
  - Both viremic at time of shedding
    - Shedding not independent event

# Subject 206 - viral testing (blood)





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# Toca 511 Safety

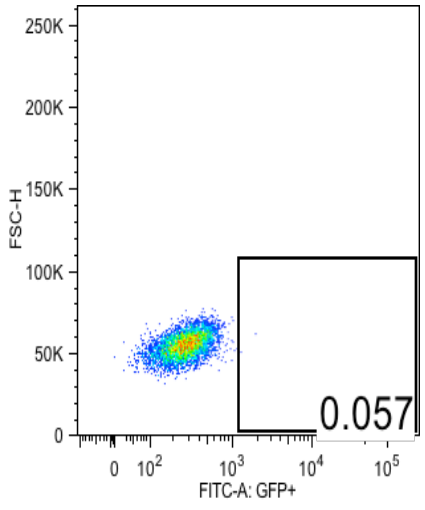
- No subject has required treatment with antiretrovirals
  - AZT, Viread, Isentress could be used if required
  - 5-FC is not the failsafe for these studies
- No health care worker has experienced inadvertent exposure to vector

# Rationale for I.V. delivery

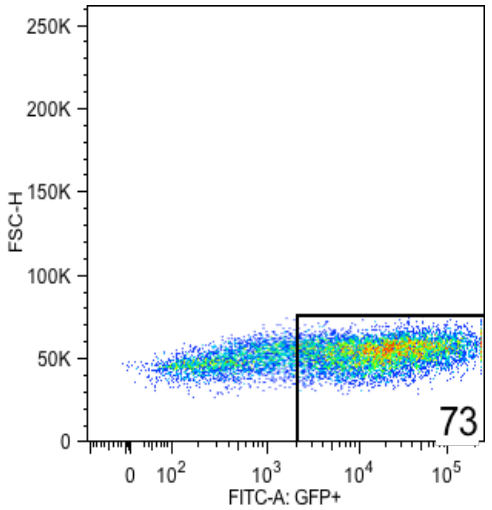
- Glioblastoma often heterogenous
- Often has necrotic poorly-vascularized center
- Often has highly vascular periphery
- Hallmark of GBM/HGG is enhancement with gadolinium on MRI
- Gadolinium gets into tumor through leaky, abnormal tumor vessels
- Preclinical data suggest vector can enter tumor through these same leaky vessels

# I.V. vector transduces brain tumor

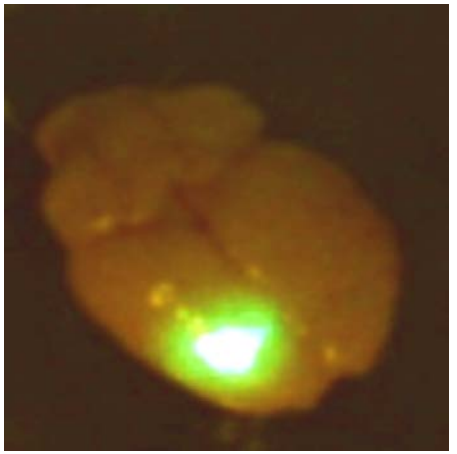
**No vector**




**IV vector**




**GFP in Brain Tumor**



Intracranial Tu2449 mouse tumor model





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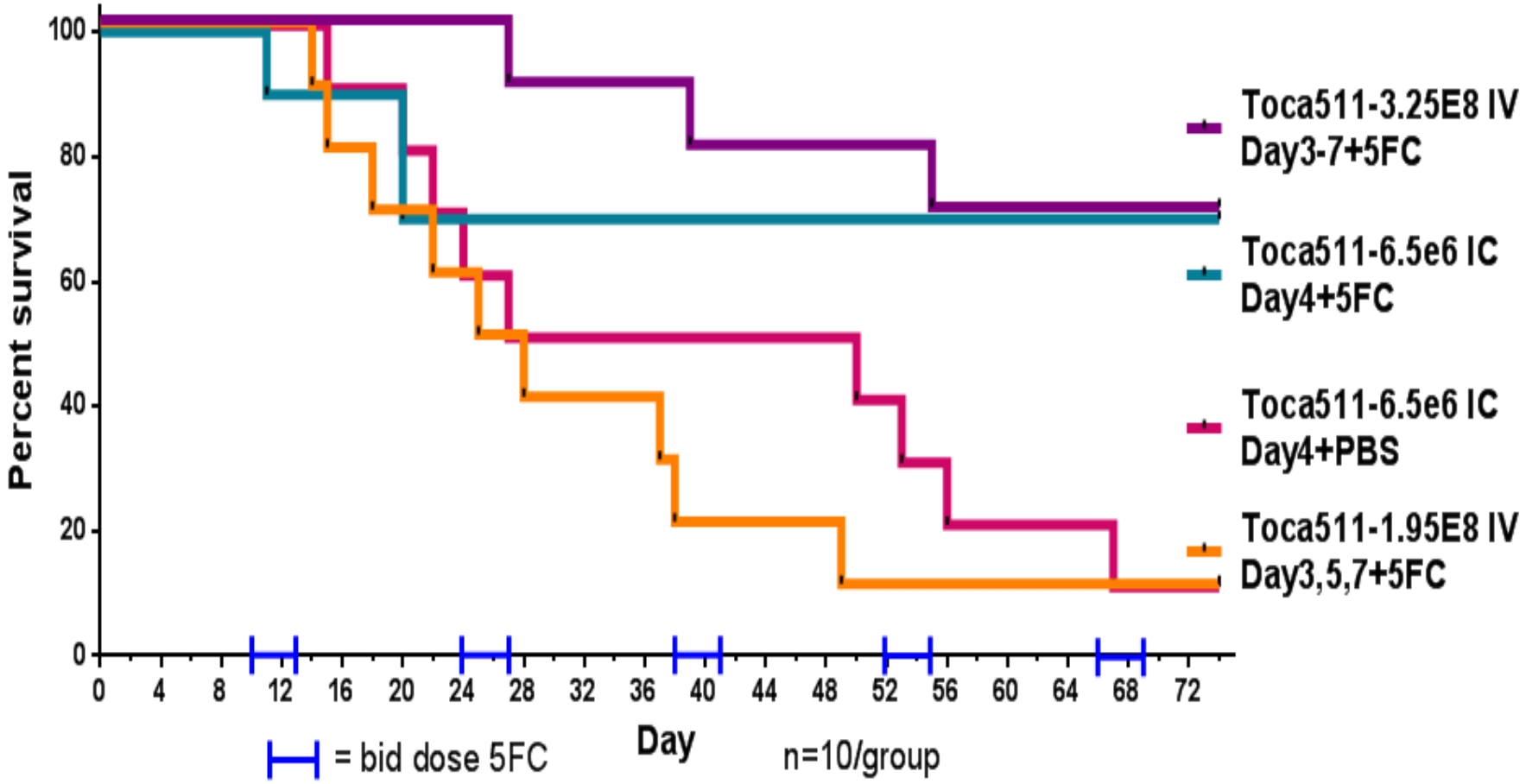
# I.V. dosing has comparable survival to I.C. dosing

Tu2449 in B6C3F1 mouse model





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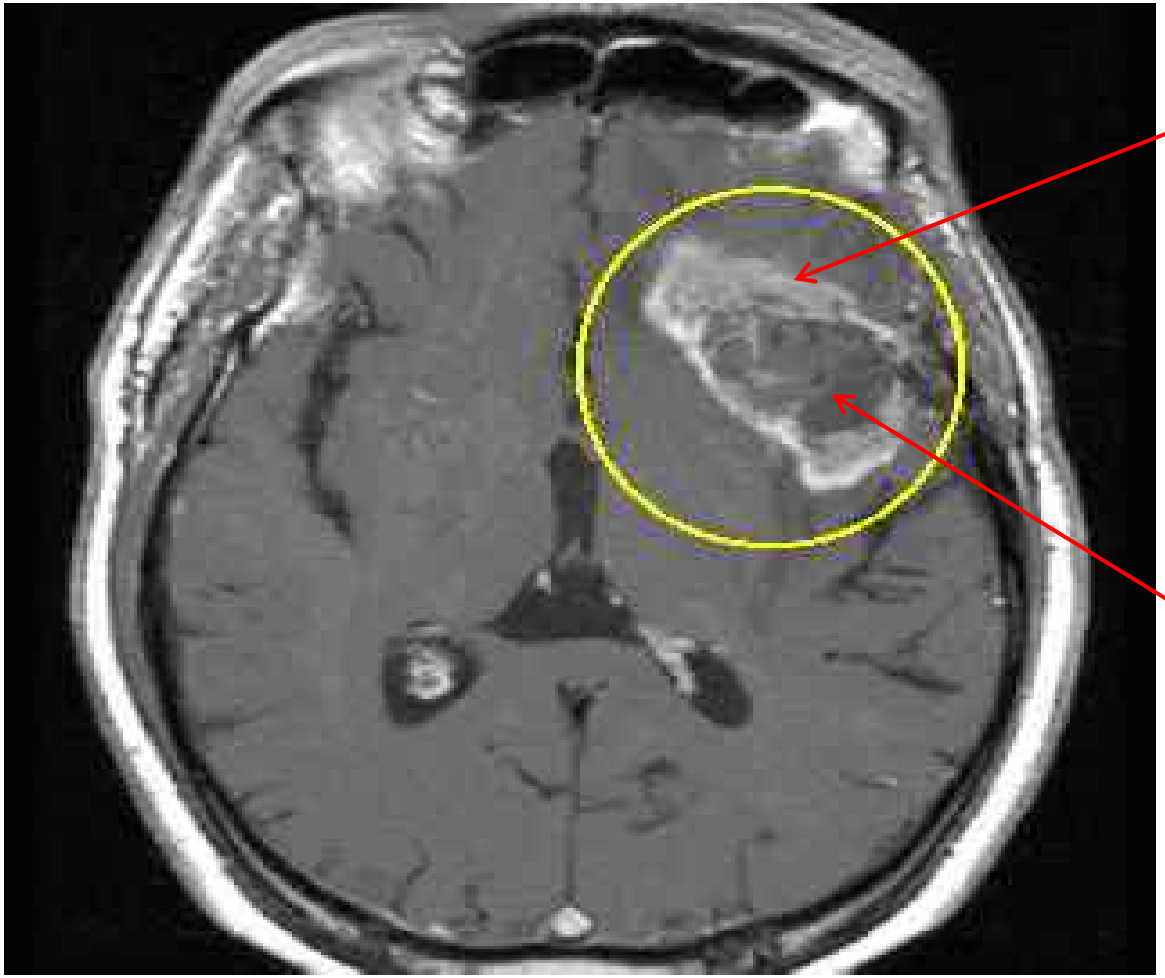
# Preclinical Safety Evaluation of I.V. Toca 511

- Toca 511 administered I.V. to mice & dogs
- BALB/c mice have immune tolerance to MLV
  - Develop lymphoma after I.C. or I.V. dosing
  - Similar clinical observations, gross pathology, biodistribution with I.V. compared to I.C. delivery of vector
  - No lymphoma observed when mice also received 5-FC
- B6C3F1 mice do not develop lymphoma or other toxicity after I.V. dosing
- Dogs had no lymphoma/toxicity after I.V. dosing
- I.V. doses given to mice are ≈3-4 logs > human starting dose

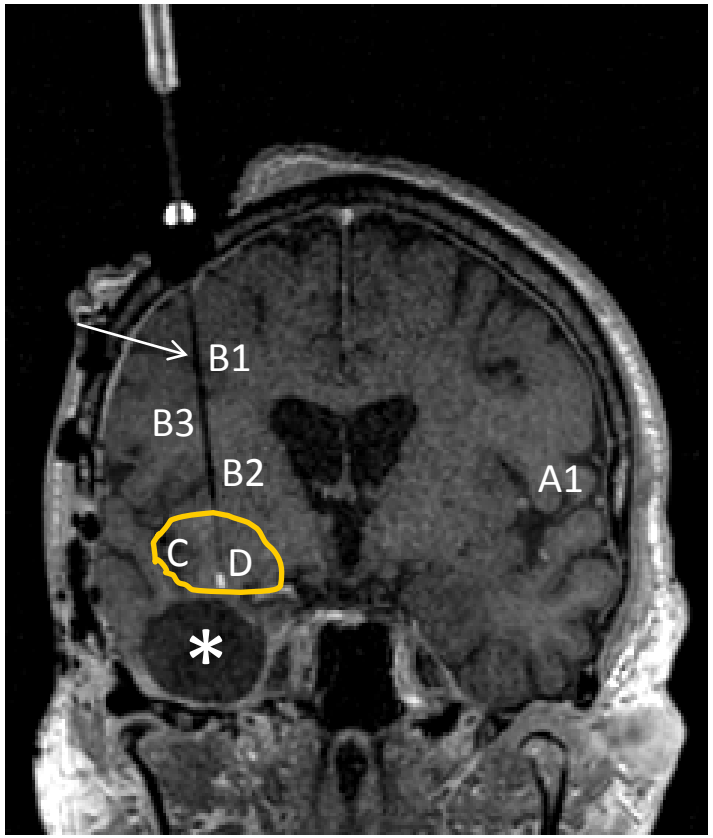
# Enhancing GBM



Vascular, enhancing periphery

Avascular, nonenhancing center

# Successful delivery of Toca 511 into center of GBM




| Sample | MLV qPCR (LLOQ 10 DNA copies/µg) | yCD2 qPCR (LLOQ 250 DNA copies/µg) |
|---|---|---|
| A1 | ND | ND |
| B1 | ND | ND |
| B2 | ND | ND |
| B3 | ND | ND |
| C1 | ND | <LLOQ |
| C2 | ND | <LLOQ |
| D1 | 98,700 | 95,500 |
| D2 | 8,570 | 7,340 |





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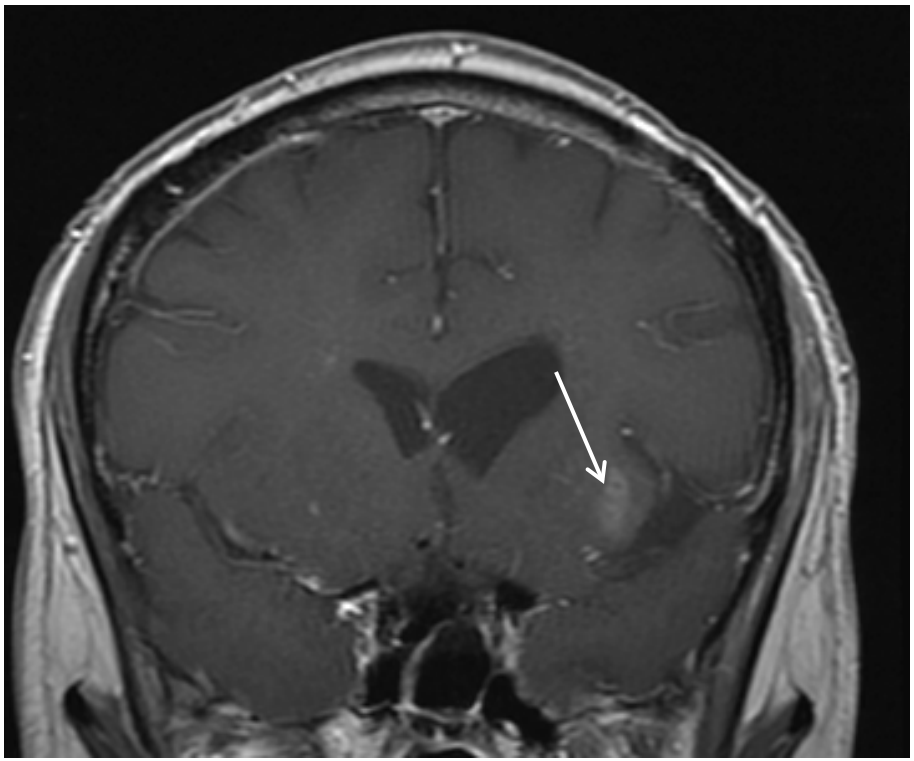
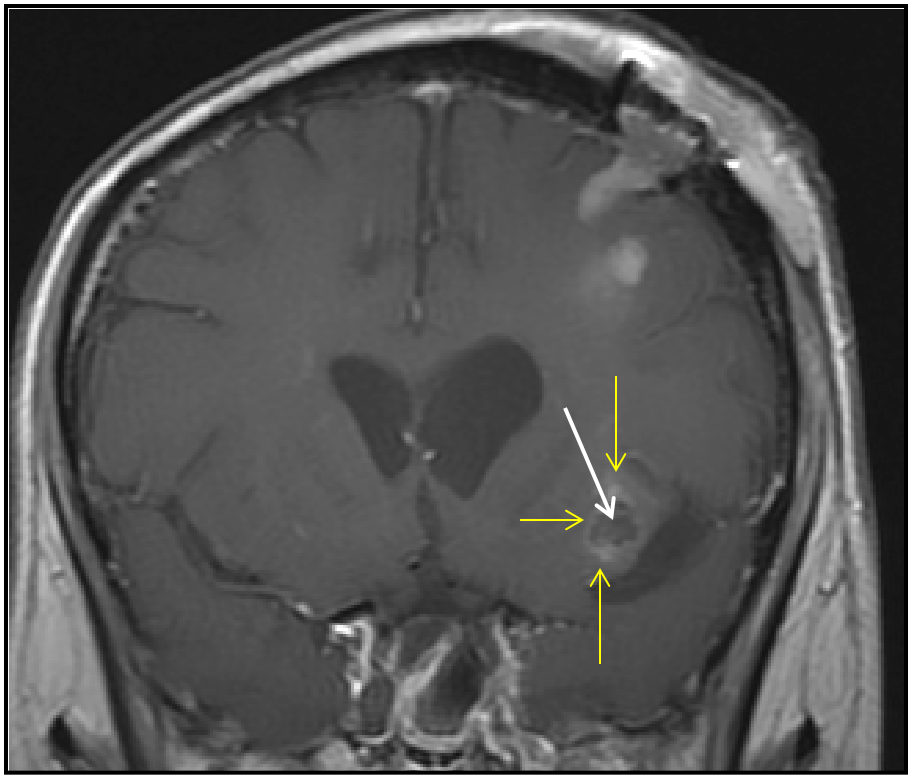
# Central tumor necrosis after injection of Toca 511 and 1 cycle of 5-FC









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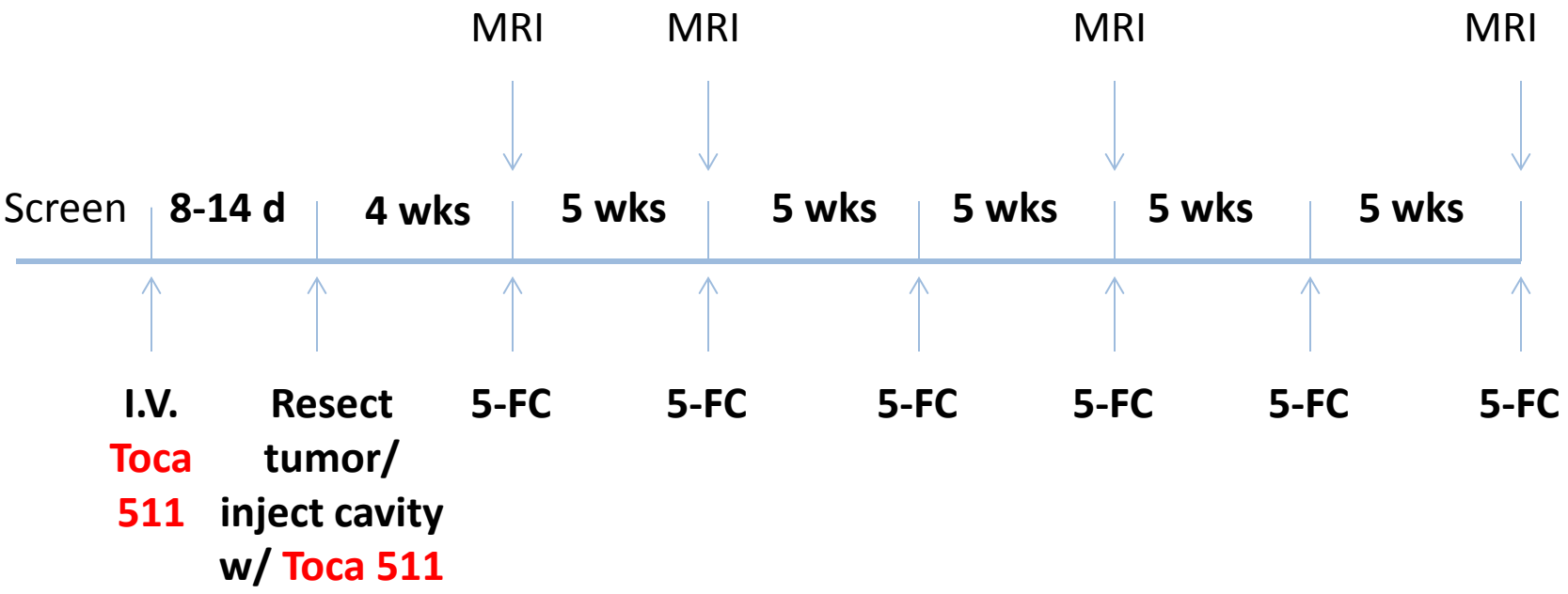
# Aim of I.V. delivery

- Target the vascular, rapidly expanding periphery of tumor
- Deliver vector without need for complex neurosurgical intervention
- Obtain quick readout of outcome by resecting tumor ≈ 11 days after I.V. administration
- Ultimately can combine with intratumoral Rx

# Design of I.V. Study

- Multicenter, P1, ascending dose study
- Adult subjects with rHGG undergoing repeat resection
- Starting dose is highest safe/tolerated dose in ongoing P1 studies (3.2 x 10^5 TU/g)
- Dose is split with ½ given I.V. and ½ given at time of resection

# Study Schematic





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# Dosing Summary

| Cohort | # subjects Planned | # I.V. injections | Total I.V. dose TU (TU/mL blood) | Total I.C. dose TU/g brain |
|---|---|---|---|---|
| 1 | 1 | 1 | 2.4 x 10^8 (4.8 x 10^4) | 1.6 x 10^5 |
| 2 | 1 | 1 | 1.0 x 10^9 (2.0 x 10^5) | 3.2 x 10^5 |
| 3 | 1 | 1 | 4.3 x 10^9 (8.6 x 10^5) | 3.2 x 10^5 |
| 4 | 3 | 3 | 1.5 x 10^10 (2.9 x 10^6) | 3.2 x 10^5 |
| 5 | 3 | 5 | 4.8 x 10^10* (9.5 x 10^6) | 3.2 x 10^5 |

* Scales to ≈20 fold lower dose than that administered to mice

# Summary

- Toca 511/5-FC delivered to 47 subjects
- Safe and well tolerated to date
- All subjects have controlled virus w/o antiretroviral Rx
- Able to successfully target center of tumor
- Need to deliver vector to vascular periphery
- Preclinical data support use of I.V. delivery
- rHGG still has poor prognosis - risk/benefit +

# Thank You